REMARKS

Claims 36 and 38-59 were pending in the instant application as of the issuance of the Office Action dated June 20, 2006. According to the foregoing amendments, claims 36 and 38-59 are cancelled without prejudice to the prosecution of these claims in this or a subsequently filed application. New claims 60-77 have been added. Accordingly, after the amendments presented herein have been entered, claims 60-77 will remain pending in this application.

Support for the introduction of new claims may be found throughout the specification and in the claims as originally filed. Specifically, support for the new claims can be found throughout the specification as originally filed, for example, page 24, line 20 to page 25, line 23 and page 34, line 14 to page 35, line 22 of the specification and in the claims as originally filed, for example, claims 1-35.

No new matter has been added by the introduction of the new claims. The introduction of new claims should not be construed as an acquiescence to the validity of the Examiner's rejections and were done solely in the interest of expediting prosecution and allowance of the claims. Applicants reserve the right to pursue the claims as originally filed in one or more further applications.

Claim Rejections – 35 USC § 112, second paragraph

Claims 36 and 38-59 are rejected under 35 U.S.C. 112, second paragraph, as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention."

Specifically, the Examiner rejects claims 36 and 49 as failing to "set forth any active method steps involved in the method/process." In addition, the Examiner rejects claims 36 and 49 for use of the phrases "capable of affecting" and "capable of binding to," respectively. Claims 38 and 50 are further rejected for use of the phrases "left wall" and "right wall". Claims 38-40 and 50-52 are further rejected as failing to provide a reference SEQ ID NO or protein sequence. Claim 42 is rejected for use of the phrase "conventional organic synthesis." Lastly, Claims 41 and 43-48 are rejected "because it is unclear as to how a skilled artisan would know *a priori* that the compound 'designed' by the method of claim 36 would agonize or inhibit LTA4

hydrolase or treat a disease." Solely in the interest of expediting examination and in no way acquiescing to the validity of the Examiner's rejections, Applicants have introduced new claims 60-77 which render the foregoing rejections moot. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejections.

Claim Rejections – 35 USC § 112, first paragraph (Written Description)

The Examiner has further rejected claims 36 and 38-59 under 35 U.S.C. § 112, first paragraph as allegedly "failing to comply with the written description requirement." Applicants respectfully traverse this rejection and submit that based on the teachings in Applicants' specification as well as the general knowledge available in the art at the time of the filing of the present application, one of ordinary skill would understand that Applicants were in possession of the claimed invention. In the interest of clarity, Applicants will address each aspect of the Examiner's rejection below.

Rejection of Claims 36 and 38-48 Directed to "Functional Equivalent Part[s]"

Initially, the Examiner is of the opinion that

> [a] description of a protein three-dimensional model, i.e., "functional equivalent part thereof", using functional language, i.e., "capable of exhibiting enzymatic activity", in the absence of a specific structure is not considered sufficient to show possession of the claimed invention. It is noted that the instant specification discloses the full-set of structural coordinates of LTA4H as set forth in Table 9, used in the claimed method. However, the instant specification does not disclose the structure coordinates of LTA4H as directed to the "functional equivalent part thereof". The examples in the specification do not provide written basis for a three-dimensional model having the limitation of "functional equivalent part thereof" from the three-dimensional structure of the full-length LTA4H; in essence, the specification simply directs those skilled in the art to go figure out for themselves what the claimed "functional equivalent part thereof" looks like. The instant specification fails to satisfy the written description requirement wherein a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention.

Applicants respectfully disagree. Applicants submit that based on the teachings in the specification and the general knowledge in the art at the time of the filing of the present

application, one skilled in the art would appreciate that Applicants were in possession of the claimed invention. For example, Applicants submit that the specification teaches the active sites of the LTA_4 hydrolase (see page 12, line 11 to page 14, line 14 of the specification). Indeed, the specification teaches a basic amino-peptidase binding site, a leukotriene binding site and a general catalytic domain for the M1 class of enzymes. Accordingly, "functionally equivalent part[s]" are sufficiently described both structurally (*i.e.*, in terms of the particular residues) and functionally (*i.e.*, in terms of activity, for example, binding or catalytic activity, associated with those particular residues).

Notwithstanding the foregoing and solely in the interest of expediting examination, Applicants have introduced new claims 60-77 which are not directed to "functional equivalent part[s]," thereby rendering the foregoing rejection moot. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection of claims 36 and 38-48 as lacking written description.

Rejection of Claims 43-48, 53 and 55-59 Directed to a Genus of Drugs/Compounds

The Examiner further rejects claims 43-48, 53 and 55-59 on the grounds that

> claims 43-48, 53 and 55-59 encompass a genus of drugs/ compounds defined only by their intended use/function, i.e., treating or preventing a wide range of disorders. There is no evidence that there is any *per se* structure/function relationship between the disclosed bestatin, the specific inhibitors of Example 3 (i.e., thiolamine and hydroxamic acid), and any others that might be found using the claimed method that are useful in treating/preventing a wide range of disorders as encompassed by claims 43-48, 53 and 55-59. There is no description of an actual reduction to practice, each step of the claimed method or distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention.

Applicants respectfully disagree. Applicants respectfully submit that the genus of compounds is sufficiently supported by the specification. Initially, Applicants submit that Applicants have characterized three inhibitors and their associations with the LTA4 hydrolase, *i.e.*, bestatin, hydroxamic acid or thiolamine. Moreover, with respect to the particular indications, Applicants submit that one skilled in the art, in view of the teachings of the specification and the general knowledge in the art at the time of the invention, would appreciate that LTA_4 hydrolase is involved in the pathogenesis of the recited indications. Accordingly, one

skilled in the art would appreciate that those compounds that bind to LTA_4 hydrolase exhibit certain activity in the treatment of those recited indications.

Notwithstanding the foregoing, solely in the interest of expediting examination and in no way acquiescing to the validity of the Examiner's rejections, Applicants have introduced new claims 60-77 that are not directed to particular indications, thereby rendering the foregoing rejection moot. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection of claims 43-48, 53 and 55-59 as lacking written description.

Claim Rejections – 35 USC § 112, first paragraph (Enablement)

The Examiner has further rejected claims 36 and 38-59 under 35 U.S.C. § 112, first paragraph as "not reasonably provid[ing] enablement for all structural coordinates defining a molecular structure of a functional equivalent [of] the human LTA4 hydrolase protein." Applicants respectfully traverse this rejection and submit that based on the teachings in Applicants' specification as well as the general knowledge available in the art at the time of the filing of the present application, one of ordinary skill in the art would be able to make and use the claimed invention using only routine experimentation. In the interest of clarity, Applicants will address each aspect of the Examiner's rejection below.

Rejection of Claims 36, 38-40 and 49-52 Directed to "Functional Equivalent Part[s]"

The Examiner rejects claims 36, 38-40 and 49-52 on the ground that

> [i]n the absence of adequate guidance and working examples by which to derive all other three-dimensional coordinates of 'functional equivalent [parts] thereof' one of skill in the art would be required to utilize inventive skill for such derivation by identifying or designing molecular structures of a 'functional equivalent [part] thereof' through the formulation of independent decisions and judgments about the criteria(s)/ parameter(s), and to test & validate these derived polypeptides. Such independent decisions, judgments, tests, & validation are not routine and is considered undue experimentation.

Applicants respectfully disagree. Applicants submit that based on the teachings in the specification and the general knowledge in the art at the time of the filing of the present application, one of skill in the art would be able to make and use the claimed invention using

only routine experimentation. For example, as set forth above, Applicants submit that the specification teaches certain active sites of the LTA_4 hydrolase (see page 12, line 11 to page 14, line 14 of the specification), such that one skilled in the art would be able to design functionally equivalent parts of the LTA4 hydrolase using only routine experimentation.

Notwithstanding the foregoing and solely in the interest of expediting examination, Applicants have introduced new claims 60-77 that are not directed to "functional equivalent part[s]," thereby rendering the foregoing rejection moot. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection of claims 36, 38-40 and 49-52 as lacking enablement.

Rejection of Claims 43-48, 53 and 55-59 Directed to a Genus of Drugs/Compounds

The Examiner further rejects claims 43-48, 53 and 55-59 on the ground that

> claims 43-48, 53 and 55-59 encompass a genus of drugs/ compounds defined only by their intended use/function, i.e., treating or preventing a wide range of disorders, wherein the relationship between the structural features of the members of the genus and said use/ function have not been defined. In the absence of such a relationship either disclosed in the as-filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition. The fact that one could have identify/design [*sic*] a compound of interest using the claimed methods does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that might be particularly disclosed in an application) would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity/ function as encompass[ed] by claims 43-48 and 53-59.

Applicants respectfully disagree. Applicants respectfully submit the identification of those drugs active for the recited indications would be well within the ability of a skilled artisan without necessitating undue experimentation. For example, Applicants submit that, in view of the teachings of the specification and the general knowledge in the art at the time of the invention, it would be routine for a skilled artisan to test the ability of identified and/ or designed compounds that bind to LTA4 hydrolase to treat the recited indications.

Notwithstanding the foregoing, solely in the interest of expediting examination and in no way acquiescing to the validity of the Examiner's rejections, Applicants have introduced new claims 60-77 that are not directed to particular indications, thereby rendering the foregoing

rejection moot. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection of claims 43-48, 53 and 55-59 as lacking written description.

Claim Rejections – 35 U.S.C. § 103

Claims 36, 38-41 and 43-59 have been rejected as being obvious under 35 U.S.C. § 103 over Balaji *et al.* (U.S. Patent No. 5,579,250) (hereinafter referred to as "Balaji"). Specifically, the Examiner is of the opinion that

> Balaji teaches methods of rational drug design via computer modeling. Specifically, columns 11-32 detail the use of atomic coordinates of a receptor – such as a protein – wherein drugs or compounds which interact therewith are designed using structural coordinate data obtained from, *e.g.*, X-ray crystallography. Polypeptide modeling is specifically discussed in column 24, line 50, through column 25, line 26.... These descriptions are encompassed by the instant methods, only missing the specific structural coordinates as disclosed in Table 9.
>
> In *Gulack* and *Ngai*, the court held that nonfunctional descriptive material in a claim does not distinguish the prior art in terms of patentability. The key factor in analyzing the obviousness of these claims over the prior art is the determination that the computer algorithm used to identify compounds that may bind LTA4 hydrolase protein is a known algorithm and is unmodified. If the difference between the prior art and the claimed invention as a whole is limited to descriptive material stored on or employed by a machine, it is necessary to determine whether the descriptive material is functional descriptive material or nonfunctional descriptive material. In this case, the structural coordinates disclosed in Table 9 are nonfunctional descriptive material. In this case, the structural coordinates disclosed in Table 9 are nonfunctional descriptive material and the method uses a known unmodified computer algorithm. Data, which are fed into a known algorithm whose purpose is to compare or modify those data using a series of processing steps, do not impose a change in the processing steps and are thus nonfunctional descriptive material. A method of using a known comparator for its known purpose to compare data sets does not become non-obvious merely because new data becomes available for analysis. Nonfunctional descriptive material cannot render non-obvious an invention that would have otherwise been obvious.

Applicants respectfully disagree. To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success

must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed.Cir. 1991), quoting *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988)).

Applying the foregoing standard to the present invention, Applicants submit that one skilled in the art would not have a reasonable expectation of success in arriving at the claimed invention. Applicants submit that the purification and crystallization procedures to arrive at the atomic coordinates of the LTA_4 hydrolase were not routine such that one skilled in the art would have a reasonable expectation of success in arriving at the claimed invention. Indeed, as described in the specification, there are major challenges for even a skilled artisan to arrive at a three-dimensional structure of a protein molecule. As taught in the specification,

> [t]here are two major difficulties in obtaining a three-dimensional structure of a protein molecule. The first one is to grow crystals of good quality that are reproducible and diffract to atomic resolution (beyond 2.5 A). This means a thorough and cumbersome investigation of parameters that influence the crystal growth such as pH, temperature, nature of buffers, nature of precipitant, just to mention a few. The addition of ligands such as substrate analogues or inhibitors or the addition of the other molecules can be important for obtaining good crystals. There is only little understanding of the physical background of the crystallization process which means that the search for suitable crystallization conditions for a certain protein is unique, requires creativity and intuition, and is governed by trial and error procedures. The purity of the protein is also a crucial parameter in the crystallization and a suitable degree of purity can be hard, or even impos[s]ible, to achieve. The second major difficulty is associated with overcoming the phase-problem which is inherent to X-ray diffraction methods. To be able to overcome this problem it is necessary to substitute the protein with suitable heavy atom substance such as e.g. mercury, gold or platinum compounds. Crystals often cannot withstand the treatment with these compounds and the search for suitable substitutions is not straight forward and may become very exhaustive. (see page 4, line 16 to page 5, line 3 of the specification).

Accordingly, one skilled in the art would not have a reasonable expectation of success in arriving at the claimed invention. Indeed, achieving high quality crystals and further overcoming the phase problem would render a skilled artisan doubtful of achieving the claimed invention.

Moreover, the Court of Appeals for the Federal Circuit has held that

> [w]hile absolute certainty is not necessary to establish a reasonable expectation of success, *In re O'Farrell*, 853 F.2d 894, 903-904, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988), there can be little better evidence negating an expectation of success than actual reports of failure. *See, e.g., In re Rinehart*, 531 F.2d 1048, 1053-54, 189 USPQ 143, 14849

(CCPA 1976). (*Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 65 USPQ2d 1961 (Fed. Cir. 2003)).

In view of the foregoing, Applicants submit that prior attempts to arrive at the claimed invention failed. Indeed, as described in the specification (see page 4, line 8 to page 5, line 16), attempts by Tsuge *et al.* (*J. Mol. Biol.* 238:854-856 (1994)) to crystallize the LTA4 hydrolase resulted in crystals that only diffracted to medium resolution. Moreover, Tsuge did not overcome the phase problem.

For at least the foregoing reasons, Applicants submit that one skilled in the art would not have a reasonable expectation of success in arriving at the claimed invention at the time of the filing of the present application, as required to establish a prima facie case of obviousness. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of the pending claims under 35 U.S.C. § 103.

CONCLUSION

In view of the foregoing remarks, reconsideration of the rejections and allowance of all pending claims is respectfully requested. If there are any remaining issues or if the Examiner believes that a telephone conversation with Applicants' Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

The Commissioner is hereby authorized to charge any deficiency in the fees paid herewith, or credit any overpayment, to Deposit Account No. 12-0080, under Order No. PVZ-006US, from which the undersigned is authorized to withdraw.

Dated: December 22, 2006

Respectfully submitted,

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